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Enantioselective palladium catalyzed allylic substitution of acyloxypyrrolinones by alcohols

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Chiral non-racemic acyloxypyrrolinones are converted into alkoxyppyrrrolinones with retention of configuration by a palladium catalyzed allylic substitution; this comprises a key step in a short chemo-enzymatic route to acyliminium ion precursors.

Enantiomerically pure alkoxyppyrrrolinones have been shown to be facile building blocks for a variety of stereoselective syntheses involving Diels–Alder cycloadditions, 1,3-dipolar reactions, conjugate additions and acyliminium ion intermediates.¹ In particular application in the asymmetric synthesis of alkaloids, based on *N*-acyliminium ion chemistry, is of great current interest.² For example, (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one [compound (–)-**3a** (*R*² = *Pr*ⁱ) in Scheme 1] has been used by Hiemstra and Speckamp as an intermediate in the synthesis of gelsemine.³ However, the stereoselective synthesis from (*S*)-malic acid⁴ is laborious and more practical routes would be desirable.

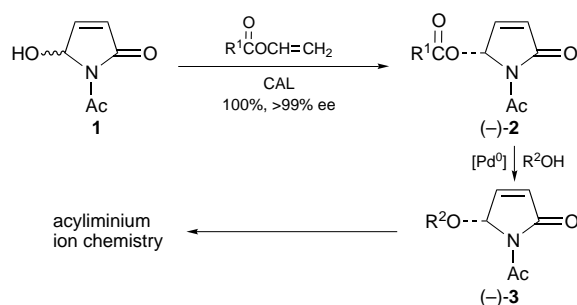
Recently we reported simple and efficient enzymatic methodology to obtain enantiomerically pure acyloxypyrrolinones **2** from hydroxypyrrolinones **1**.⁵ In this process both enantiomers of an acyloxypyrrolinone can be obtained by the same enzyme (*Candida antarctica* lipase, CAL) using either an esterification (Scheme 1) or a transesterification. Although these compounds

have been applied with success in various stereoselective transformations,⁶ they are not suitable as acyliminium ion precursors. In order to generate an acyliminium ion the acyl group on nitrogen must be removed.⁴ This is possible with an alkoxy group at the 5-position but not with a more sensitive acyloxy group. We now report that the enzymatic method can be combined with a palladium catalyzed allylic substitution to generate optically active alkoxyppyrrrolinones, which can readily be transformed to acyliminium ion precursors.⁴

When a solution of (*R*)-(–)-**2a** (*R*¹ = Me) in *Pr*ⁱOH is stirred at room temperature for 7 h in the presence of 0.5 mol% Pd(PPh₃)₄, 5-isopropoxy derivative (*R*)-(–)-**3a** (*R*² = *Pr*ⁱ) is obtained in 99% yield with 95% ee (Table 1, entry 1).‡ The optically active acyloxypyrrolinone is thus converted into optically active alkoxyppyrrrolinone, *via* Pd⁰ catalyzed allylic substitution with *Pr*ⁱOH as the nucleophile, with nearly complete retention of configuration. An allyl palladium intermediate **5** (Scheme 2) is presumably involved. When the reaction was performed in the presence of Pd(OAc)₂ (5 mol%) and PPh₃ (20 mol%) the reaction rate was appreciably lower (90% conversion after 3 d at 20 °C, >95% ee). An essential feature is that the nucleophile *Pr*ⁱOH is also used as a solvent (roughly 13 M). In the presence of an additional solvent like THF (*Pr*ⁱOH *ca.* 10^{–1} M) no product was obtained after 18 h at room temp. When the allylic substitution was performed at higher temperatures, the reaction was very fast, but the enantioselectivity decreased in the course of the reaction (Table 2). This depletion of ee might be due either to loss of stereochemical integrity of the allyl palladium intermediate or partial racemization of acyloxypyrrolinone **1** or alkoxyppyrrrolinone **3**.

The substitution using Pd(PPh₃)₄ can easily be performed on a gram scale with equal efficiency (99%) and selectivity (94% ee). A lower rate was observed in the presence of additional PPh₃, probably because the equilibrium for the oxidative addition of the palladium complex is shifted to the left (Scheme 2).⁷ The effect on the enantioselectivity is negligible.

When EtOH was used instead of *Pr*ⁱOH as a nucleophile the reaction was much faster, probably because of the higher

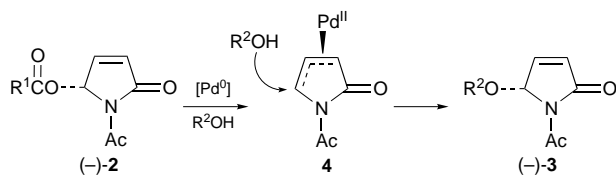


Scheme 1

Table 1 Pd catalyzed nucleophilic substitution of (–)-**2** (>99% ee)

Entry	R ¹	R ²	T/°C	Catalyst	t/h	Conversion ^a (%)	Ee ^b (%)
1 ^c	Me	<i>Pr</i> ⁱ	25	Pd(PPh ₃) ₄ (0.5%)	7	99	95
2 ^c	Me	<i>Pr</i> ⁱ	25	Pd(PPh ₃) ₄ (0.5%)	5.5	72	97
3 ^c	Me	Et	18	Pd(PPh ₃) ₄ (5%)	1	100	93
4 ^d	Allyl	<i>Pr</i> ⁱ	20	Pd(OAc) ₂ + PPh ₃ (5%)	63	100	83
5 ^d	C ₉ H ₁₉	<i>Pr</i> ⁱ	20	Pd(OAc) ₂ + PPh ₃ (10%)	63	40	84
6 ^d	Bu ^t	<i>Pr</i> ⁱ	20	Pd(OAc) ₂ + PPh ₃ (5%)	48	29	95
7 ^d	Ph	<i>Pr</i> ⁱ	20	Pd(OAc) ₂ + PPh ₃ (5%)	18	33	93
8	Me	<i>Pr</i> ⁱ	25	Pd(MeCN) ₂ Cl ₂ + PPh ₃ (5%)	21	100	89
9	Me	<i>Pr</i> ⁱ	25	Pd(MeCN) ₂ Cl ₂ (5%)	3	99	> 99
10	Me	Et	25	Pd(MeCN) ₂ Cl ₂ (5%)	3	94	99

^a The conversion was determined by GC. ^b The ee of **3** was determined by chiral GC; >99% indicates that the other enantiomer could not be detected. ^c (+)-**2** (>99% ee) was used as starting material. ^d The ee of starting material **2** is unknown.



Scheme 2

Table 2 Pd catalyzed nucleophilic substitution of (+)-**2a** ($R^1 = \text{Me}$) at 70°C^a

Entry	<i>t</i> /min	Conversion ^b (%)	Ee ^c (%)
1	5	43	90
2	25	91	79
3	40	100	75

^a $\text{Pd}(\text{OAc})_2 + \text{PPh}_3$ (5%) was used as catalyst, Pr^iOH was used as solvent.

^b The conversion was determined by GC. ^c The ee of (+)-**3a** ($R^2 = \text{Pr}^i$) was determined by chiral GC.

solubility of the substrate in this solvent. A slight decrease in selectivity (93% ee) was observed (Table 1, entry 3).

This reaction can also be performed with acyloxypyrrolinones with other acyl groups (Table 1, entry 4–7). The optically active starting materials were obtained *via* enzymatic esterification, analogously to our reported procedure.⁵ Because a method for direct ee determination of these 5-acyloxypyrrolinones has not yet been found, the palladium catalyzed allylic substitution and subsequent ee determination of the 5-isopropoxy pyrrolinone provides a useful alternative for determination of the ee of the starting materials.

Other palladium catalysts were also examined as the use of $\text{Pd}(\text{PPh}_3)_4$ did not result in complete stereoselectivity (95–97% ee). $\text{Pd}(\text{Bn})(\text{PPh}_3)_2\text{Cl}$ gave, under the same conditions in Pr^iOH , less than 5% conversion in 23 h (71% ee), whereas with $\text{Pd}(\text{dppe})_2$ no product was obtained. Palladium(II) complexes such as $\text{Pd}(\text{OAc})_2$ were also tested without PPh_3 . In this case the reaction did not proceed, but surprisingly when LiCl was added 22% conversion was found after 23 h (42% ee). A mixture of $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ (5 mol%) and PPh_3 (20 mol%) was also used, but although this reaction was faster than with $\text{Pd}(\text{OAc})_2$ and PPh_3 (100% conversion in 21 h), the selectivity was not improved (Table 1, entry 8). A remarkable improvement was achieved when $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ (5 mol%) was used without PPh_3 . With this catalyst the reaction is fast, quantitative and proceeds with complete stereoselectivity (Table 1, entries 9, 10). On 0.5 g scale with 5 mol% Pd^{II} catalyst, 96% yield of (*S*)-**3a** ($R^2 = \text{Pr}^i$, 99% ee) was obtained.

Palladium catalyzed nucleophilic substitution reactions of allylic substrates have found widespread use in organic

synthesis and although a variety of nucleophiles has been employed emphasis has been on carbon–carbon bond formation.⁸ On the contrary the use of alcohols as nucleophiles in Pd catalyzed allylic substitution is rare, because alcohols are generally considered poor nucleophiles. The few reported examples⁹ are often either intramolecular substitutions or make use of derivatives of alcohols. The quantitative and stereoselective Pd catalyzed allylic substitution of 5-acyloxypyrrolinones by alcohols provides a key step in the new catalytic enantioselective, lipase and palladium based methodology for the preparation of enantiopure alkoxy-pyrrolinones.

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Notes and References

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‡ Ee's were determined with a Hewlett Packard 5890 GC, equipped with a capillary column coated with CP cyclodextrin B-2,3,6-M-19 (for **3a**, $R = \text{Pr}^i$) or with a 30 m \times 0.25 mm capillary column (ASTEC G9409-15) coated with B-TA (β -cyclodextrin, trifluoroacetyl) (for **3b**, $R = \text{Et}$).

Selected data for **3a**: $[\alpha]_{\text{D}}^{25} -149$ (c 0.5, CHCl_3); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.15 (d, 3 H, J 8.8), 1.18 (d, 3 H, J 8.8), 2.49 (s, 3 H), 4.23 (sept, 1 H, J 6.1), 5.92 (d, 1 H, J 2.0), 6.06 (d, 1 H, J 6.1), 6.97 (dd, 1 H, J 2.0, 6.1); $\delta_{\text{C}}(\text{CDCl}_3)$ 22.8 (q), 23.0 (q), 24.9 (q), 73.0 (d), 86.3 (d), 126.8 (d), 147.7 (d), 168.7 (s), 170.0 (s).

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